

# WHEN TO MEASURE BLOOD GLUCOSE - COHORT-SPECIFIC GLYCAEMIC CONTROL

Ulrike Pielmeier\*, Steen Andreassen and J. Geoffrey Chase  
Center for Model-based Medical Decision Support  
Aalborg University  
Fredrik-Bajers-Vej 7, E4-215  
9220 Aalborg, Denmark  
email: upiel@hst.aau.dk

## ABSTRACT

Model-based control systems are better fitted to glycaemic control in intensive care than ad-hoc protocols, but depend on predictive accuracy and facilitation of clinical routines. A general method to customize and visualize model-based blood glucose predictions is presented. Customization is based on admission type and diabetic status of patients. Blood glucose concentrations of 14 critically ill patients from two intensive care units were retrospectively predicted. Relative prediction errors were found to be highest for diabetic I and II patients, and lowest for non-diabetic trauma and head-injured patients. Standard deviations of mean relative prediction errors are proposed to be used for display of accuracy of model-based blood glucose predictions in prospectively controlled patients. The method provides for an optimized timing of blood sampling to facilitate tight glucose management in the ICU.

## KEY WORDS

Control Systems, Medical Decision Support, Physiological Modelling, Critical Care, Model-based Control, Hyperglycaemia

## 1 Introduction

Intensive insulin therapy and carbohydrate-reduced meals are suggested solutions to normalize blood glucose in hyperglycaemic intensive care patients [1],[2],[3],[4]. Ad-hoc sliding scale protocols based on clinical experience are commonly used to determine the required amount of insulin. However, no standard protocols or metrics have been established, which is why blood glucose target ranges vary between hospitals or even locally between intensive care wards [5]. Moreover, ad-hoc protocols require a tight schedule of highly frequent blood glucose measurements to capture rapidly changing patient conditions [6]. Such schedules require additional resources, thus increasing the clinical burden and bear the risk of non-compliance and failure [7].

Methods based on metabolic models are patient-specific and provide better control in critical care patients than ad-hoc protocols [8]. Model-based control methods enable the prediction of blood glucose outcomes for con-

current glycaemic interventions such as insulin therapy or nutritional changes. The quality of model-based control depends highly on prediction accuracy and on how such methods are able to overcome the need for highly frequent measuring [9].

This research presents a general method to customize model predictions to patient subgroups. The customized predictions are used to display the prediction accuracy over time in a graphical user interface. The graphical display enables visual glycaemic control within target ranges self-defined by a department or hospital. The method provides for a per-patient based timing of blood glucose measurements to replace fixed high-frequency schedules.

## 2 Methods

Data from 14 patients from two independent intensive care units in Aalborg, Denmark and Christchurch, New Zealand are gathered retrospectively. For this research, the patients are grouped according to admission type and diabetic status. The first group constitutes of five patients from Aalborg with either trauma or head-injury and no prior history of diabetes. The second group is a cross-sectional mix from Aalborg and Christchurch with two cardiac and three medical patients, and no prior diabetes. In the third group are two diabetes I patients from Christchurch, and two diabetes II patients from Aalborg and Christchurch. Two in this group have trauma, one is a general surgical patient, and one is a medical patient.

Glycaemic control followed local department rules. Arterial cannula blood samples had been taken. In Aalborg patients, blood samples were analysed with an ABL700 blood gas analyzer. GlucoCard glucometers were used in Christchurch. These latter sensors have a larger 7 – 10% standard error. In both ICUs, insulin was administered as intravenous infusion of fast-acting insulin, in rare cases patients received an additional sub-cutaneous bolus injection. Five of eight Aalborg patients and all patients from Christchurch were exclusively fed via a feeding tube; three Aalborg patients received an intermittent intravenous glucose infusion.

Blood glucose concentrations for the three groups are predicted retrospectively using the Glucosafe model. Glu-

cosafe is a decision-support system based on the metabolic model derived from Arleth et. al. [10] that adapts dynamically to different patient condition and evolution. Based on information about past blood glucose measurements, insulin therapy and nutrition, the model determines two patient specific parameters that are used for model predictions.

Predictions are done by moving forward along the blood glucose measurements of each patient. At each measurement, blood glucose concentrations are calculated over the following 8.5 hours; then the actual measurements in that time period are paired with their respective predicted values, and the forward prediction times per measured/predicted value pair are recorded.

The logarithm of the ratio of measured over predicted blood glucose concentration gives a relative prediction error, with a normal distribution and zero mean. Per patient group, the root mean square (RMS) log relative prediction error over prediction time interval is calculated from

$$RMS = \sqrt{\frac{1}{n} \sum_{i=1}^n \left( \ln \frac{m_i(t)}{p_i(t)} \right)^2} \quad (1)$$

where  $m_i$  and  $p_i$  are the  $i$ th measured and predicted blood glucose concentration, respectively, and  $n$  is the number of predictions per interval. Curves are fitted to the RMS log relative prediction errors of each cohort. Values on each fitted error curve translate into the standard deviation from mean relative prediction error and are dependent of patient group, metabolic model employed, and prediction time.

The standard deviations from mean relative prediction error yield a range of a maximum and a minimum value for each predicted blood glucose concentration in prospectively controlled patients. If there is allowance for an error range of two standard deviations, the range can be calculated from

$$2\sigma(t) = \ln \frac{bg_{\max}(t)}{bg_{\text{pred}}(t)} \quad (2)$$

$$-2\sigma(t) = \ln \frac{bg_{\min}(t)}{bg_{\text{pred}}(t)} \quad (3)$$

where  $\sigma(t)$  is the standard deviation from mean relative prediction error,  $t$  is the prediction time,  $bg_{\text{pred}}(t)$  is the model-predicted blood glucose concentration, and  $bg_{\max}(t)$  and  $bg_{\min}(t)$  are the maximum and minimum blood glucose concentrations.

Model-predicted blood glucose concentrations and ranges can be displayed on a prediction time axis in prospectively controlled patients. Intersections with pre-defined bounds of blood glucose concentrations yield the time for the next blood glucose measurement.

### 3 Results

Figure 1 shows the fitted prediction error standard deviations for the three patient groups. Non-diabetic trauma and

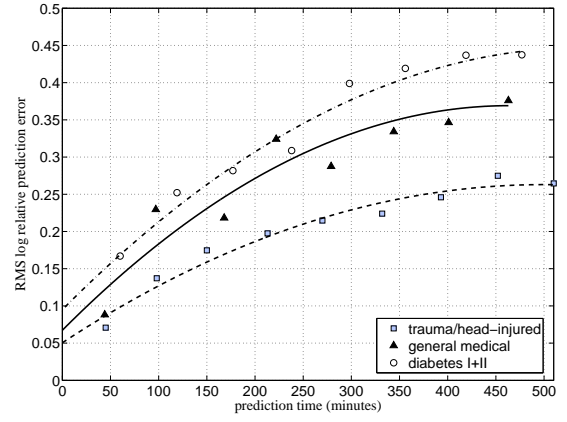


Figure 1. Root mean square (RMS) log relative prediction error over prediction time. Lines show the fitted prediction error by cohort: Trauma and head-injured patients (dashed) had lowest and diabetes I+II patients (dash-dot) had highest prediction errors. The solid line is the prediction error fit for a broad cross-section of medical and cardiac patients without diabetes.

head-injury patients have lowest relative prediction errors, followed by cardiac and medical patients, and diabetic I+II patients with highest prediction errors. Both trauma and diabetic patients show a clear trend towards steadily rising, saturating curves.

Among patients from Aalborg, mean standard deviations for predictions up to 300 min tend to be lower in trauma patients (0.133, 0.160, 0.165, 0.173, 0.215) when compared to cardiac or medical patients (0.208, 0.285) and the type 2 diabetic trauma patient (0.263) in the group.

Differences are not as pronounced among Christchurch patients. Mean standard deviations are high for the two type I diabetic patients (0.287, 0.327) compared to cardiac and medical patients (0.173, 0.283, 0.303) and one type II diabetic surgical patient (0.178).

APACHE II scores at admission to ICU were available for the patients from Christchurch. On bivariate 2-tailed correlation analysis, higher APACHE II scores do not raise RMS log relative prediction errors.

Figures 2 and 3 show in a proof-of-concept matter the graphical output of cohort-specific model-based predictions for the cases of a diabetic patient and a trauma patient. Control limits are arbitrarily set to 3.5–7.5 mmol/L. The predicted blood glucose concentrations over the following 450 min are displayed with  $\pm 2$  standard deviations (95%) error range based on the fitted curves in Figure 1. In the case of the diabetic patient, the next measurement must occur after 1 hour (upper intersection) or 2 hours (lower intersection) to avoid going out of the targeted blood glucose range. For the trauma patient it is sufficient to schedule the next measurement after 2 hours (upper intersection) or 3 hours (lower intersection).

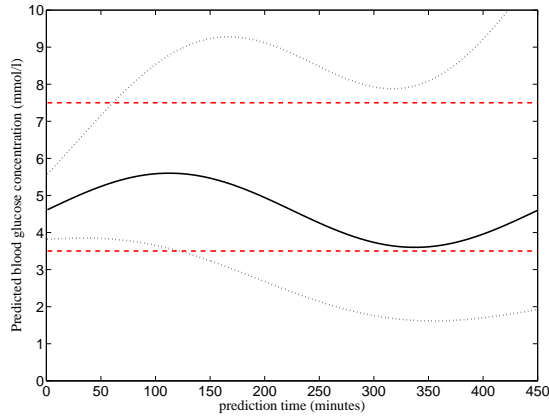


Figure 2. Proof-of-concept display of predicted blood glucose with 95% error range for a diabetic patient. Measurements must be scheduled after 1 hour to avoid going out of the desired blood glucose band. Error range is calculated from cohort-specific standard deviations in Figure 1.

Thus, cohort specific prediction error can be used with a desired control tightness (limits) to optimise glucose sample timing.

## 4 Discussion

This research presents a general method to customize and visualize model-based predictions for use in glycaemic control in intensive care. Customization is based on admission type and diabetic status. Cohort-specific prediction errors are used to enhance the graphical display of predicted outcome and accuracy of glycaemic interventions in prospectively controlled patients. The method makes the use of fixed blood sample schedules obsolete, because measurement times can be directly read off chart. The timing of measurements varies, but is depending on the metabolic model used, cohort specifics, and the blood glucose target band of the respective intensive care ward.

In this analysis, higher APACHE II scores do not raise RMS log relative prediction errors. High APACHE score patients tend to vary more greatly, and glycaemia in patients with high APACHE II scores may be more difficult to control [6]. However, APACHE is only a one time assessment after which patients may get better or worse or both over time. Prediction error is largely a function of the patients movement over the prediction interval. Thus prediction errors may well not correlate as the APACHE may no longer be true some time after admission. To get a better picture of the relationship it takes consecutive assessments of patient condition and potential variability over several days. With the data available, no final conclusion on the influence of APACHE scores can be drawn.

Trauma patients without diabetes had lowest prediction errors. Since all analysed patients received sedatives,

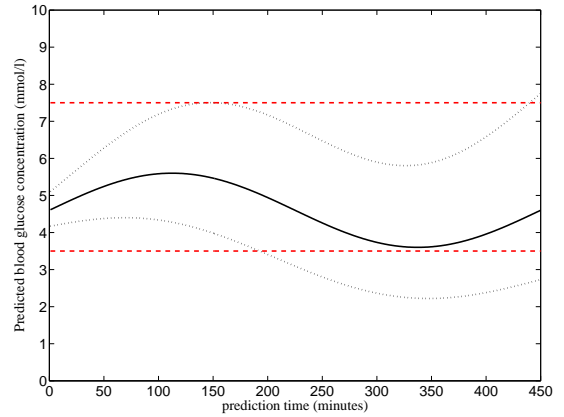


Figure 3. Graphical output for optimised glucose sampling in a trauma patient. To stay in the desired range, measurements must be scheduled in 2 hours (upper limit) or 3 hours (lower limit).

medication alone is not the decisive factor for this observation. Typically, trauma patients are younger and healthier and more likely to be getting better without developing sepsis, ARDS or pneumonia. Thus, they are likely to vary less than older, diabetic, already critically ill patients. Another aspect is that delayed gastric emptying is highly prevalent (up to 80%) in trauma and head-injury patients [11] and has a likely effect on the uptake of carbohydrates [12],[13]. This could indirectly be linked to a better predictability of these patients.

Predictions on diabetes type I and II patients yielded highest prediction errors, though results may be biased by the fact that this group contained only four patients with a highly mixed disease background (two trauma, one surgical and one medical patient). However, the lack of endogenous insulin production in type I diabetics is expected to have unsteading effects on blood glucose. This is in addition to the beforehand low insulin sensitivity in these patients, that enhances small variabilities into bigger changes in blood glucose for a given intervention.

Differences in blood sample analysis caused differing measurement errors. This is observed in the extrapolated intersections with the value axis in Figure 1. Those intersections are assumed to be approximations of mean log relative measurement error, which are lower for groups with higher precision at blood sample analysis. Therefore, an unknown portion of the cohort prediction error differences is likely to be attributed to measurement error differences. However, differences are also pronounced within groups from one ICU, and the physiological particulars in diabetics are likely causes for true differences in prediction errors.

Current results miss the comparison to predictions using other metabolic models, such as the model developed by Chase and co-workers in Christchurch [14], to filter out model-dependent effects on cohort differences. The

results of a comparison of predictive powers of the Glucosafe and the Christchurch model [15] indicate the existence of model-independent, cohort-specific differences in glycaemic predictability, though the patients were grouped by ICU instead of patient characteristics.

## 5 Conclusion

This method gives clinical staff a convenient graphical means to base decisions about glycaemic control intervals on the estimated precision of model-based predictions. The method is generalizable to any model-based glycaemic control system and any percentage likelihood for the error bands. The conclusions from cohort-specific analysis drawn here are based on too small numbers to be definitive, but merit to be studied more detailed in a larger cohort.

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